PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

(Attorney No. SIR-MIS-00001-US-CIP[4])

IN THE APPLICATION OF:	)		
	)		
McSwiggen *et al.*	)		
	)		
Serial No. 10/757,803	)	**Examiner:**	**Bowman**
	)		
Filed: January 14, 2004	)	**Group Art Unit:**	**1635**
	)		
Title RNA Interference Mediated Inhibition of Gene Expression Using Chemically Modified Short Interfering Nucleic Acid (siNA)	)	**Confirmation No.:**	**5421**

BRIEF ON APPEAL

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BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the Final Rejection mailed November 3, 2009. This brief is submitted along with the large entity fee of $540. A notice of appeal was filed on January 12, 2010. No additional fee is believed to be due. In the event of any variance between the amounts enclosed and the Patent and Trademark Office charges, the Commissioner is authorized to charge or credit any difference to our Deposit Account No. 50-4615.

Contents

REAL PARTY IN INTEREST

The real party in interest is Sirna Therapeutics Inc., a wholly owned subsidiary of Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828). A copy of the Board's decision in attached as Appendix C.

The following US patent applications are currently on appeal and share common priority with the instant application:

USSN 11/502,875
USSN 10/693,059
USSN 11/487,788

STATUS OF CLAIMS

A Final Office Action was mailed on November 3, 2009. Claims 18-20 and 33-39 stand rejected and are presently pending. The rejections of claims 18-20 and 33-39 are appealed with this submission. A copy of the claims on appeal is attached in Appendix A.

STATUS OF AMENDMENTS

No claims are amended.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention provides certain chemically modified double stranded nucleic acid molecules, each comprising a sense strand and an antisense strand, where each strand is 18 to 27 nucleotides in length, 18-23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence; wherein the sense strand includes a terminal cap moiety at both 5' and 3' ends; and wherein 10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. *See* claim 18; Specification at, *inter alia,* page 29, line 22 to page 30,

line 7 (specifically page 30 lines 2-7); and page 32, lines 10-15. See additionally Figures 18 and 19 and Tables I & IV for numerous examples of the presently claimed chemically modified nucleic acid molecules.

Each of the molecules above can comprise no ribonucleotides, or alternately can comprise one or more ribonucleotides. *See* claims 19 and 20; Specification at, *inter alia,* page 14, lines 14-16; page 78, lines 18-28; Figures 18 and 19, and Tables I & IV.

One or more of the pyrimidine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecules can be a 2'-O-methyl pyrimidine nucleotide. *See* claim 33; Specification at, *inter alia,* page 30, lines 2-4; Figures 18 and 19 (A, B, C), Table I & IV (*e.g.,* "Stab 6").

One or more of the purine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecules can be a 2'-deoxy purine nucleotide. *See* claim 34; Specification at, *inter alia,* page 12, lines 4-7; page 18, lines 13-15; page 22, lines 4-11; page 38, lines 11-21; Figures 18 and 19 (D, F), Table I & IV (*e.g.,* "Stab 7").

One or more of the pyrimidine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecules can be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claim 35; Specification at, *inter alia,* page 30, lines 2-4; Figures 18 and 19 (A, B, C, D, E, F), Table I & IV (*e.g.,* "Stab 3", "Stab 4", "Stab 7", "Stab 12", and "Stab 18").

One or more of the pyrimidine nucleotides in the antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claim 36; Specification at, *inter alia,* page 30, lines 2-4; Figures 18 and 19 (A, B, C, D, E, F), Table I & IV (*e.g.,* "Stab 5", "Stab 8", "Stab 11", "Stab 13", "Stab 14", "Stab 15", "Stab 19", "Stab 20", and "Stab 21").

One or more of the purine nucleotides in the antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-O-methyl purine nucleotide. *See* claim 37; Specification at, *inter alia,* page 12, lines 11-14; page 18, lines 20-25; page 22, lines 16-19; page 39, lines 12-32; Figures 18 and 19 (E), Table I & IV (*e.g.,* "Stab 8" and "Stab 19").

The present invention also pertains to a composition comprising one of the molecules depicted above in a pharmaceutically acceptable carrier or diluent. *See* claim 38; Specification at, *inter alia,* page 19, lines 30-31.

Each of the modified double stranded nucleic acid molecules can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages. *See* claim 39; Specification at, *inter alia,* page 30, lines 5-6; Figures 18 and 19, and Tables I & IV.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are:

(I) Whether claims 18-20 and 33-39 are indefinite under 35 U.S.C. § 112, second paragraph, due to an alleged lack of antecedent basis for the term "10 or more pyrimidine nucleotides".

(II) Whether claims 18-20 and 33-39 introduce new matter under 35 U.S.C. § 112.

(III) Whether claims 18-20 and 33-39 are obvious under 35 U.S.C. § 103(a) over Elbashir *et al.* (2001, EMBO J., v. 20(23): 6877-88), in view of Matulic-Adamic *et al.* (U.S. 5,998,203), Parrish *et al.* (2000, Molecular Cell, v. 6: 1077-1087) and Crooke (US 5,898,031).

(IV) Whether claims 18-20 and 33-39 require a terminal disclaimer in view of the provisional obviousness-type double patenting rejection over Applicant's USSN 10/923,536.

ARGUMENT

I. Claims 18-20 and 33-39 are not indefinite

The Office alleges that because Claim 18 recites the limitation "10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified" in part (d) of the claim, and because the preceding portion of the claim does not require for *each strand* to comprise 10 or more pyrimidine nucleotides, that there is insufficient antecedent basis for this limitation in the claim. *See* Office Action at page 4. Applicants respectfully traverse and conclude that the Office has misconstrued the instant claims and has premised its finding of indefiniteness on that misconstruction.

Claim 18 reads:

A chemically modified double stranded nucleic acid molecule, wherein:

a) the double stranded nucleic acid comprises a sense strand and an antisense strand;

b) each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence;

c) the sense strand includes a terminal cap moiety at its 5'- and 3'-ends; and

d) 10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides.

First, claim 18 *does not require* that *each* strand comprise 10 or more pyrimidine nucleotides. Rather, claim 18 requires that "10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides", as opposed to "10 or more pyrimidine nucleotides of the sense strand and 10 or more pyrimidine nucleotides of the antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides". Because part (a) of the claim calls for a sense strand and an antisense strand, and because part (b) of the

claim requires that each strand is 18 to 27 nucleotides in length and 18-23 nucleotides of each strand are complementary, then it follows that the sense strand and antisense strand together must have at least 18 pyrimidine nucleotides, and that under part (d) of the claim, 10 or more of these pyrimidine nucleotides are modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. As such, the limitation of "10 or more pyrimidine nucleotides" is not lacking in terms of antecedent basis and cannot lead to a finding of indefiniteness under 35 U.S.C. § 112, second paragraph.

II. Claims 18-20 and 33-39 enjoy the benefit of the priority documents of record and do not introduce new matter

The Office declined to afford the previously submitted claims a priority before the filing date of the instant application. *See* Office Action at page 2. Applicants respectfully traverse, however, it should be noted that an earlier priority date is not needed to address the outstanding Obviousness rejection. With respect to new matter, Applicants provide the following arguments, which serve to address the priority issue as well as the new matter rejection because the Office has used the same reasoning in denying priority and in alleging new matter.

The Office alleges that "[a]lthough applicant points to support for the instant chemical modifications of claim 18 at page 30, lines 2-7 (as well as in the priority documents", [this] passage begins with 'In another embodiment', and is not disclosed in combination with the instant size limitations or with the limitations of claims 19, 34, or 37." Office Action at pages 3 and 5. Applicants respectfully traverse, and assert that there is a clear showing of possession of the claimed invention not only at the time of filing the instant application, but also as is evidenced in the priority documents of record. Such evidence of possession is found in the plain language of two paragraphs of the specification and in hundreds of representative examples shown in the Tables and Figures of both the instant application as filed, and also in the priority documents of record. Specifically, the paragraph of the specification spanning pages 29 and 30 of the application as filed features a double stranded nucleic acid molecule having certain enumerated chemical modifications, and the paragraph of the specification starting on

page 32, line 10 of the application as filed, provides for the length of the strands *of any chemically modified double stranded nucleic acid molecule of the invention.*

The paragraph spanning pages 29 and 30 of the instant application reads; (see also paragraph spanning pages 9 and 10 of USSN 60/358,580, filed February 20, 2002):

> In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. **In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides**, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Literal support for the limitation (d) in claim 18 is shown in bold. As such, limitation (d) is drawn from the embodiment set forth in the paragraph beginning on page 29, line 22, which specifies a siNA molecule having particular numbers and combinations of enumerated modifications. The sentence beginning at page 30, line 2, specifies one or more pyrimidine modifications in combination with one or more phosphorothioate internucleotide linkages and/or terminal cap modifications..

The paragraph starting at page 32, line 10 of the instant application reads; (see also last paragraph on page 11 of USSN 60/358,580, filed February 20, 2002):

> In another embodiment, **a chemically-modified siNA molecule of the invention comprises** a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27

(*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII.

Here, the plain language clearly refers to the fact that **any chemically modified siNA duplex of the invention** can have strands that are 18 to 27 nucleotides in length and 18 to 23 base pairs, so long as the modification comprises a structure having any of Formulae I-VII. Each and every modification of the claims is included in these Formulae. For example, the phosphorothioate modification is clearly included in Formula I (see page 24 of the application as filed and page 5 of USSN 60/358,580 filed February 20, 2002). The 2'-deoxy, 2'-O-methyl, and 2'-deoxy-2'-fluoro modifications are clearly included in Formula II (see page 25 of the application as filed and page 6 of USSN 60/358,580 filed February 20, 2002). Terminal cap modifications are clearly included in Formulae V, VI, and VII (see pages 35-36 of the application as filed and pages 12-13 of USSN 60/358,580 filed February 20, 2002). Thus, because this paragraph refers to *any siNA molecule of the invention*, this paragraph is not an isolated embodiment, but rather an embodiment that further specifies additional limitations (length, number of base pairs etc.) of the invention as presently claimed. Likewise, the limitations of claims 19, 34, and 37 are all described in embodiments that refer to "**a siNA molecule of the invention**" having additional limitations and do not stand in isolation. *See* page 14, lines 14-16 (with reference to claim 19); page 12, lines 4-7 (with reference to claim 34); and page 12, lines 11-14 (with reference to claim 37). In addition, these limitations in combination are found in numerous representative examples described throughout the specification, Tables, and Figures.

To better illustrate this point, Applicant has reproduced portions of **Table IV** of the instant application. This table summarizes modification strategies of certain double stranded nucleic acid molecules of the invention as presently claimed: "the chemically modified constructs described in **Table IV** can be applied to **any siNA sequence of the invention**." Application page 83, lines 29-30. For example, **Table IV** specifies stabilization chemistries with certain combinations of features as presently claimed, specifically ***modified pyrimidines (2'-fluoro, 2'-O-methyl, or 2'-deoxy), CAPS (at the 3'***

and 5' ends of the sense strand), phosphorothioates, and purines (modified or unmodified), as shown below:

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S

CAP = any terminal cap, see for example **Figure 22**.

All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues

All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.

S = sense strand

AS = antisense strand

As discussed above, the present claims define an invention that was clearly conveyed to those skilled in the art at the time the application was filed (as well as in the priority documents of record). The claims have not been amended in such a way to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed. One of skill in the art would readily appreciate that Applicants were in

possession of the claimed invention at the time of filing the instant application (and at the time of filing the priority documents of record), as is evidenced by the plain language of the specification as filed, the priority documents as filed, and as is clearly shown in the hundreds of representative examples of the presently claimed double stranded nucleic acid molecules provided therein. Thus, the Office's finding of new matter under 35 U.S.C. § 112, first paragraph, is improper.

III. Claims 18-20 and 33-39 are inventive and not obvious

The present invention results from the discovery of certain chemically modified double stranded nucleic acid molecules that are both highly serum stable and active in mediating RNA interference. The state of the art at the time of the invention only provided double stranded nucleic acid molecules that were useful as research tools *in vitro* due to a lack of serum stability. The present invention advanced the prior art to allow for the use of such molecules *in vivo*, and more importantly, in therapeutic applications. The Office has asserted that this significant advancement over the prior art resulted merely from "routine optimization", and alleges that the invention is *prima facie* obvious. Specifically, claims 18-20 and 33-38 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Elbashir (The EMBO J. 2001, Vol. 20 (23), 6877-6888), in view of Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, Vol. 6, 1077-1087), and Crooke (U.S. 5,898,031). *See* Office Action at page 3. Applicant respectfully traverses, and relies upon well established jurisprudence as discussed below to prove otherwise.

The Office alleges that "[i]t would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal," and that "[r]outine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art." Office Action at page 12. Applicants respectfully

traverse, and maintain that the presently claimed invention cannot be obvious for at least three reasons.

First, one of skill in the art would *not have had any reasonable expectation of success* in practicing the claimed invention at the time of the invention because the prior art either taught away from the claimed invention, or indicated a high level of unpredictability that would have precluded any reasonable expectation of success. Second, it is impermissible hindsight to conclude that the present invention is obvious because it would have been "obvious to try" the combinations of known modifications using "routine optimization," especially since the prior art gave *"no direction as to which of many possible choices is likely to be successful"* and offered *"only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988). Finally, even if a *prima facie* finding of obviousness can be established, the *failure of others*, along with the *surprising results* obtained in practicing the invention, serves to effectively rebut any such presumption of obviousness.

1. No reasonable expectation of success

One of skill in the art at the time of the invention would not have had any reasonable expectation of success in practicing the claimed invention because the cited prior art references taught away from the claimed invention and suggested a high level of unpredictability with respect to the claimed features.

The Office maintains that the Elbashir reference does not teach away from the instant invention, and alleges that the teachings of Elbashir *et al.* and the other cited references would provide a "reasonable expectation of success given that each of the modifications were known in the art at the time of the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes". Office Action at page 12. The Office supports this position by stating that "the results of Elbashir *et al.* are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage." Office Action at page 13. However, this analysis ignores

the fact that Elbashir *et al.* provides a clear warning against making the modifications encompassed by the pending claims (e.g., beyond the use of 2'-deoxy at the 3'-termini of the duplex).

Elbashir's teachings of modified short double stranded nucleic acid molecules with ***retained activity*** are limited to duplexes having from two to four 3'-terminal 2'-deoxy modifications per strand, as represented pictorially below (note, circles = pyrimidine nucleotides, i.e. U, T, or C; squares = purine nucleotides, i.e. A or G; shaded circles or squares = 2'-deoxy nucleotides):

All other modified constructs made by Elbashir had "abolished RNAi" activity. In *'The siRNA user guide'* portion of the Discussion section (page 6885; emphasis added), the authors conclude the following:

> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

Applicant maintains that this is a very strong teaching away from producing more extensively modified duplexes, as described in the pending claims. The plain language of *'The siRNA user guide'* portion of the Elbashir reference clearly states that more extensive 2'-deoxy or 2'-O-methyl modifications, i.e. modification beyond two to four 3'-terminal deoxynucleotide substituations in each strand are to be avoided. The duplexes

currently claimed, requiring a sense strand with 3' and 5' terminal cap moieties *in addition to* 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications, comprise without question the type of "more extensive" modification that Elbashir warns against. Thus, from the clear teachings of Elbashir, those skilled in the art would most certainly not have any reasonable expectation of success in modifying double stranded nucleic acid molecules "more extensively", i.e., beyond the 3'-terminal position of each strand with 2'-deoxy modifications, and subsequently retaining RNAi activity.

The Office incorrectly asserts that Elbashir does not teach away from the instant invention, or in the alternative only teaches away from 100% modification of one or both strands (which, should be noted, is presently required by claim 19). In this regard, the position taken by the Office that Elbashir offers "motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage" (Office Action at pages 13-14) cannot be reconciled with the clear warning against "more extensive modifications" published by this leading group of researchers who pioneered early characterization of double stranded nucleic acid molecules. Indeed, the Federal Circuit held in *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314 (Fed. Cir. 2009) that a prior art reference teaches away from the claimed invention if a combination would not have worked *for the intended purpose* of the claimed invention, specifically where "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." 567 F. 3d. at, 1325-28. Furthermore, where insight of an inventor is contrary to the understanding and expectations of the art, a structure effectuating it would not have been obvious. *Schenck v. Nortron Corp.*, 713 F.2d 283, 785 (Fed. Cir.1983). The Supreme Court in KSR emphasized the key importance of a teaching away reference, stating that, "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be non-obvious." *KSR Int'l Co.* 127 S. Ct. 1727, 1740 (2007 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Clearly, proceeding when there is a teaching away supports non-obviousness, not motivation. See also, MPEP §2145 ("proceeding contrary to accepted wisdom is evidence of non-obviousness").

In addition to ignoring the existing jurisprudence on teaching away, the Office continues to incorrectly assert that "Elbashir *el al.* is evidence that modification is well tolerated in the terminal portions of the duplex, offering further motivation to modify the terminal regions" because "the modifications were tolerated on the one end, one would have been motivated to incorporate them on the other end". Office Action at page 16. The Office further asserts that "Elbashir offers motivation to modify terminal nucleotides and Matulic-Adamic *et al.* teaches the benefit of a plethora of terminal cap moieties and teaches incorporation of such moieties at 5' and 3' ends." Office Action at page 20. However, in each and every instance where Elbashir modified the 5'-end of one or both strands, activity was abolished. Clearly, based on the teachings of Elbashir, one of skill in the art, at the time of the invention, even armed with the teachings of Matulic-Adamic, would not have been so motivated as to modify both the 3' and 5' ends of one or both strands, and certainly would not have any reasonable expectation of success in doing so *in combination with* 10 or more modified pyrimidine nucleotides.

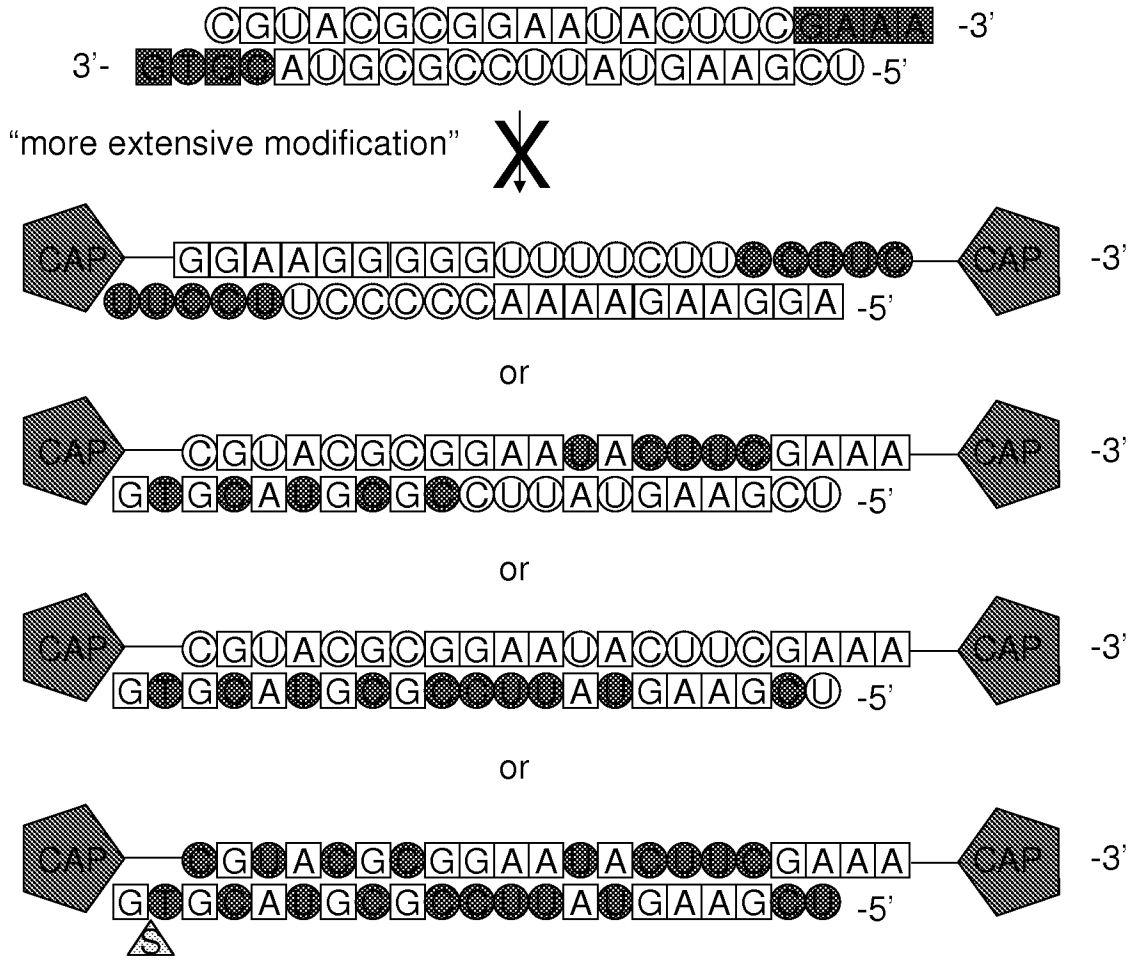
The Parrish reference, published prior to the Elbashir reference and sharing common authors, does not remedy the shortcomings of Elbashir, let alone the strong teaching away provided therein. In fact, the Parrish reference provides additional teachings away. The Office continues to mischaracterize the teachings of Parrish, stating that "Parrish *et al.* teaches extensive modification of a long dsRNA with 2'-deoxy pyrimidine modifications with resultant interference activity." Office Action at page 17. However, in the alternative, Parrish teaches away from incorporating 2'-deoxy modifications as they were found to be detrimental to RNAi activity, a point that continues to be entirely ignored by the Office. Specifically, Parrish teaches that modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand produced a substantial decrease in interference activity. ("A second position at which modifications were tested was the 2' position of the nucleotide sugar. Modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand of the trigger was sufficient to produce *a substantial decrease* in interference activity (Figure 5B)." Parrish, at page 1081, right column.)

Parrish also teaches away from applying more than one phosphorothioate modification to different nucleotide bases because incorporation of more than one phosphorothioate base modification greatly reduced RNAi activity, while incorporating more than two phosphorothioate base modifications abolished RNAi activity. Thus, at best, Parrish teaches optimization type experiments that utilize one uniform modification at a time, failing to show any combinations. The Office requests clarification on this point, alleging that "the statement by applicant is not evident upon a review of the document and particularly at page 1084." Office Action at page 1. In response, *quoting directly from Parrish*, "RNAs with two [phosphorothioate] modified bases also had *substantial decreases in effectiveness* as RNAi triggers (data not shown); modification of *more than two residues greatly destabilized the RNAs in vitro and we were not able to assay interference activities*." Parrish at page 1084, emphasis added.

In view of the deficiencies of Elbashir, Matulic-Adamic and Parrish, Applicants stress that the Office uses impermissible hindsight analysis to support the assertion that one of skill in the art would have had a reasonable expectation of success in generating highly modified duplexes that retain RNAi activity. This is highlighted by the Office's reliance on the Crooke reference. Crooke was cited as effectively teaching "walking modifications across antisense oligonucleotides to optimize the locations of the modifications and activity of the oligonucleotide". Office Action at page 13. The Office asserts that since "Elbashir *et al.*, Matulic-Adamic *et al.*, and Parrish *et al.* teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir *et al.* is considered within the realm of routine optimization." Office Action at page 13. However, it is important to recognize that after actually performing walking modifications, as described by Crooke, across one or both strands of the duplex, Elbashir concluded that more extensive modifications than those described above was not favored.

Furthermore, walking experiments could not have arrived at the instant invention. If one of skill in the art performed walking experiments to optimize the closest prior art

duplex (Elbashir), *but intentionally designed the duplex in hindsight to have a continuous stretch of pyrimidine nucleotides at the 3'-ends of each strand*, he would not have arrived at the present invention which calls for positional modification at the 3' and 5' ends of the sense strand with CAP modifications, which are *in addition to* any nucleotide modifications of the duplex. Therefore, extending the expectation of success in practicing the present invention in view of the teachings of Elbashir, Matulic-Adamic, Parrish, and Crooke, is improper as is shown below.



Importantly, as is shown in the examples above, the invention does *not* call for the positional modification of non-terminal nucleotides of the duplex, but rather sequence-specific modifications based on the *type* of nucleotide, i.e. pyrimidine, in addition to the 3' and 5' terminal CAP requirements which are positional. Thus, combining the structural characteristics disclosed by Elbashir, Matulic-Adamic, and/or Parrish with the

methodology described in Crooke simply does not provide any motivation or reasonable expectation of success in arriving at the instantly claimed invention. The Office's conclusion clearly demonstrates the use of hindsight (as addressed below) in attempting to arrive at the presently claimed invention, and completely ignores both the teaching away aspects of Elbashir and the high level of unpredictability that existed at the time of the invention. Thus, there is nothing in Crooke or Matulic-Adamic to remedy the shortcomings or teaching away that is evident in both Elbashir and Parrish, who succeeded only minimally in applying one type of modification at a time up to the point of failure, never even venturing to mix different modifications together. The proposition that one of skill in the art, armed with the teachings of Elbashir, Parrish, Matulic-Adamic, and Crooke, would be motivated and have a reasonable expectation of success in arriving at the present invention therefore cannot stand.

2. ***"Obvious to try" analysis under In re Kubin in view of In re O'Farrell precludes any finding of obviousness***

Applicant maintains that no *prima facie* showing of obviousness can stand in view of the strong teaching away and resulting high level of unpredictability that is evident from a plain reading of the Elbashir reference, which represents the closest prior art at the time of the instant invention. Even in the absence of the teaching away by Elbashir, Applicant maintains that no prima facie finding of obviousness can be established under an "obvious to try" analysis using current jurisprudence.

In continuing to support a finding of *prima facie* obviousness, the Office has maintained the position that "[i]t would have been prima facie obvious to perform routine optimization to determine which of the known modification or combinations of modifications are optimal" and that "one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes". Office Action at pages 12-13. The Office relies upon *In re Aller*, 105 USPQ 233 at 235 and quotes the following: "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine optimization." *Id.* It should be noted that the present invention cannot have

possibly arisen from discovery of "optimum or workable ranges by routine optimization". Rather, specific chemically modified double stranded nucleic acid compositions are being claimed that all have specific design criteria that combines various features, i.e., a duplex having 10 or more pyrimidine nucleotides modified with 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro modifications *and* a terminal cap moiety at both 3' and 5' ends of the sense strand (claim 18), *in addition to* phosphorothioate (claim 39) and specific purine and pyrimidine modifications (claims 34-37), with ribonucleotides (claim 20) or alternately up to 100% modified (claim 19). This is not an instance of optimized ranges as was attempted by Elbashir *et al.*, but rather an invention consisting of novel and non-obvious combinations of features giving rise to surprising and unexpected results where others failed.

The Office is essentially arguing that the present invention would be "obvious to try" using known modifications and routine experimentation, and is therefore *prima facie* obvious. Applicants respectfully disagree. The Federal Circuit has clarified the standard for a finding of obviousness based on an "obvious to try" standard in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.,* a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the

Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell,* at 903-04.

A reading of the cited prior art reveals a vast number of possible modifications that were available to one of skill in the art at the time of the instant invention. This large number is but a fraction of the modifications taught by the prior art as a whole, and the number and types modifications that could be applied to an siRNA is nearly infinite when one factors into consideration that the claims also require specific combinations of modifications (2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro, with CAPS, and further phosphorothioate modifications) and specific modification at certain positions (3' and 5' termini of the sense strand), and modification of certain types of nucleotides in the duplex (combinations of differentially modified pyrimidine and purine nucleotides) with a certain number of modifications (10 or more).

The claims thus require specific selections from at least *4 different criteria*: (1) the number of modifications, (2) the types of modifications, (3) the positions of modifications, and (4) the distinction of pyrimidine or purine. As was clearly shown in the Crooke reference, "routine experimentation" using walking experiments or other approaches to explore ranges to optimize stability and activity, even using hindsight, would not be expected to arrive at the instant invention which requires a specific number of a specific subset of modifications (2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro) to be applied to 10 or more pyrimidine nucleotides, *in addition to* terminal cap modifications of both the 3' and 5' ends of one strand of the duplex (as required by claim 18), *in addition to* phosphorothioate modifications (as required by dependent claim 39), in addition to specific combinations of pyrimidines and purines (as required by claims 34-37). Not only did the references cited herein provide no guidance as to what individual modifications when used "more extensively" can result in siRNA molecules that are both active and stable, they in fact indicated that extensive incorporation of these modifications into an siRNA was detrimental, or at least highly unpredictable. The prior art references therefore provide no guidance or any level of predictability that would allow one of skill in the art to have any reasonable expectation of success using *the*

combination of features as presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness as one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the instantly claimed invention.

Even if one takes the position that routine testing with known modifications and known assays would ***eventually*** lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fail to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to types of modifications one could apply to a short dsRNA molecule, providing merely a large selection of possibilities to choose from. In fact, these known modifications were individually demonstrated by those who first studied short dsRNA in the field to be sometimes feasible with limited application, but more often than not incompatible with RNAi activity. That unpredictability grows only larger if the known modifications were applied more extensively, up to 100%, and in combination, as is presently claimed. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. ***"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."*** *Kubin* at page 1359.

Therefore, this is not an instance where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful.***" *Id.* Rather, it is an instance where the prior art provides "no direction as to which of many possible choices is likely to be successful" and "only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* Most importantly (as addressed previously), the prior art, by teaching away from more extensive modification, evidenced such a high level of unpredictability prior to the instant invention so as to preclude any reasonable expectation of success in practicing the claimed invention, which calls for

both (1) more extensive modification, i.e. 10 or more positions modified; (2) positional modification, i.e. CAP modification of both 3' and 5' ends of the sense strand; (3) differential modification, i.e. modification of pyrimidines vs. purines; and (4) particular modifications that were taught to abolish activity when used "more extensively", i.e. 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success akin to one trying to arrive at the 4 digit code for a combination lock through "routine experimentation", wherein the only guidance as to the teaching of the code indicates that certain selections are to be avoided. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

Lastly, the Office refers to Giese *et al.* (US 2004/0180351) not as a reference relied upon in the instant rejection, but rather for "additional response to applicant's arguments given the effective filing date of the instant claims as set forth above". Office Action at page 21. The Giese application was filed on August 5, 2003, with priority claimed to 60/402,541, filed August 12, 2002. As such, even the earliest priority that could possibly be afforded to Giese *et al.* is after the earliest effective priority date of the instant invention, February 20, 2002 (see discussion of priority above). Nevertheless, Applicant wishes to address Giese *et al.*, in view of the Office's assertion that "Giese *et al.* is further evidence that combining modifications in regions, including the instant types of chemical modifications is a matter of routine optimization of the balance of stability/activity, and that this is a better approach than blanketing the molecule with one type of modification." Office Action at page 23.

The Giese *et al.* application has matured into US Patent No. 7,452,987, with claims directed to double stranded nucleic acid molecules with a specific pattern of alternating 2'-O-methyl modifications. Therefore, and without any acquiescence as to the patentability of the specific constructs disclosed therein, the Office's assertion that Giese *et al.* provides evidence that combining modifications is a matter of "routine optimization" to "balance stability and activity" flies in the face of the Office's own determination of patentability in that case. Furthermore, with respect to the instant

invention, even without taking priority into account, Giese does nothing to remedy the shortcomings of Elbashir, Parrish, Matulic-Adamic, and Crooke in terms of an obviousness inquiry. Giese, in referring to Figure 8 therein, teaches that "end modifications have no beneficial effects on RNAi stability" and "end protection (e.g. iB or amino) does not increase the stability in serum. In addition, it can also be concluded that, in contrast to the understanding in the art before the filing of the present application, endonucleases are more important than exonucleases in the protection of RNAi molecules". Giese, page 4, paragraph [0072] and page 14, paragraph [0169].

Importantly, Giese only teaches successful balancing of stability and activity with position specific patterns of 2'-O-methyl modification, which is applied in a rigid, sequence independent manner to any sequence, and fails to take into account pyrimidine specific modification. Therefore, in balancing stability and activity via "routine optimization", and in view of Giese, one of skill in the art would certainly not be motivated to incorporate terminal modifications to protect against exonucleases in addition to internal pyrimidine specific modifications to protect against endonucleases, let alone have any reasonable expectation of success in doing so. Consequently, even in view of the art filed *after* the date of the instant invention, a *prima facie* case of obviousness cannot stand. It is only the disclosure of the Applicant, when viewed in hindsight, which can provide the basis for the Office's assertion of obviousness.

3. ***Secondary indicia preclude any finding of obviousness***

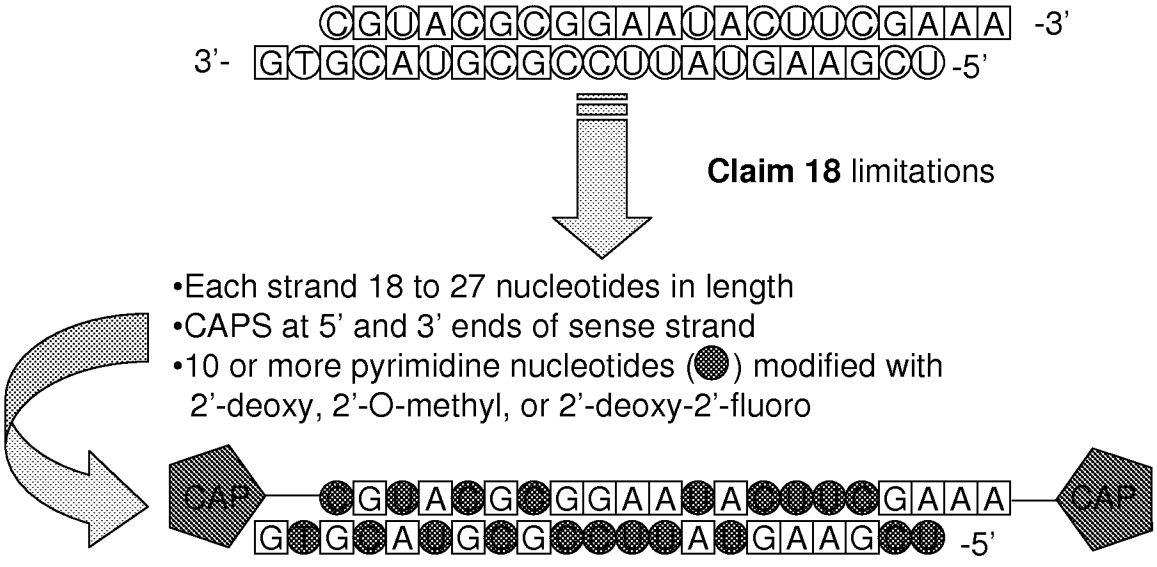
Applicant maintains that no *prima facie* finding of obviousness can stand in view of the strong teaching away that is evident from a plain reading of the Elbashir reference, and that even an "obvious to try" analysis fails because of the lack of guidance and/or predictability offered by the prior art. However, even if a *prima facie* showing of obviousness could be established, such a finding is effectively rebutted due to secondary considerations. Specifically, (1) the failure of others, coupled with (2) the surprising results obtained using the instant invention, are a clear and irrefutable demonstration of non-obviousness with respect to the presently claimed invention.

The instant invention provides double stranded nucleic acid molecules that are both highly serum stable and potent in mediating RNA interference, both *in vitro* and *in vivo*. The closest prior art is the Elbashir reference cited herein. The authors of Elbashir, armed with all of the knowledge proffered by the prior art with respect to chemical modification of nucleic acids, who conducted extensive characterization and analysis of double stranded nucleic acid molecules with respect to optimized activity, and who published a "User Guide" with respect to their findings; attempted to stabilize double stranded nucleic acid molecules, but *failed* in providing molecules that are both stable and active (see discussion below with respect to **Figure 3** of the instant application). In fact, Elbashir taught that double stranded nucleic acid molecules that were "more extensively" modified beyond 2'-deoxy modification of the 3'-terminal nucleotide positions "reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." Elbashir, at page 6885, under "The siRNA user guide." As such, the teaching of Elbashir does not provide for any chemically modified double stranded nucleic acid molecule that is both serum stable with retained (let alone improved or potent) activity.

The instant invention is a departure from the teachings of Elbashir's " siRNAUuser Guide" and provides double stranded nucleic acid molecules having key features that impart a high level of serum stability yet maintain significant, or even improved, RNAi activity compared to those of the prior art (see **Figures 3, 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87** and **Table I and IV** of the instant application, specific examples of which are described in greater detail below). These features are presently claimed. Specifically, Claim 18 requires that the sense strand have a terminal cap moiety at *both 3' and 5'-ends* of the sense strand. Claim 18 *also* requires modification *10 or more pyrimidine nucleotides of the sense and antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications*. The dependent claims provide for additional modifications as well, including phosphorothioate modifications (Claim 39), 2'-deoxy purine modifications and 2'-deoxy-2'-fluoro modifications in the sense strand (Claims 34 and 35), 2'-O-methyl purine modifications and 2'-deoxy-2'-fluoro modifications in the antisense strand (Claims 36 and 37), with ribonucleotides (Claim 20) or without ribonucleotides, thus modified up to

100% (Claim 19). In this regard, even the minimal requirements of claim 18 differ substantially from the teachings of Elbashir in terms of structure, and result in double stranded nucleic acid molecules with surprising and unexpected properties (as described below).

The Office asserts that "the claims are not directed to any specific pattern of modification that has demonstrated any unexpected property, given that the claims embrace combinations of modifications at different positions depending on the target sequences." Office Action at page 15. Applicants respectfully maintain that the invention, when properly understood, is directed to a specific and uniform "pattern" of features that can be applied to any double stranded nucleic acid sequence as described in the specification. For example, application of the features of claim 18 to any duplex sequence will result in a specific structure with well defined features that include: The length of each strand, the number of base pairs in the duplex, caps at the 3' and 5'-ends of the sense strand, and 10 or more pyrimidine nucleotides of the sense and antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of these features is illustrated pictorially below, and the surprising and unexpected properties of the molecules of the invention (high serum stability coupled with a high level of activity/potency) are described subsequently.



Application of the features of claim 18 to a double stranded nucleic acid sequence of interest provides surprising and unexpected results. These unexpected results are clearly taught by the application as filed. For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, Figure 4 on page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (See **Figure 3** of the instant application, SEQ ID NOs: 394 and 395), when tested in human serum, has a half life (T ½) of *15 seconds*. The duplexes of the instant invention however, all having 3' and 5'-caps combined with 10 or more 2'-deoxy-2'-fluoro pyrimidine modifications, all show dramatically improved nuclease stability: T ½ of *138 minutes* for SEQ ID NOs: 396 and 397; T ½ of *3.7 days* for SEQ ID NOs: 396 and 398; T ½ of *72 minutes* for SEQ ID NOs: 396 and 399; T ½ of *40 days* for SEQ ID NOs: 396 and 400; and T ½ of *32 days* for SEQ ID NOs: 396 and 401.

Additionally, the RNAi activity of duplexes of the invention, all having 3' and 5'-caps combined with 10 or more pyrimidine modifications (2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro), is surprisingly *comparable to or even improved* when compared to a control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 6" sense strand (sequence 30222, SEQ ID NO: 373) consisting of 3' and 5'-terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" antisense strands, all having 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" sense strand (sequence 30063, SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-terminal caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" antisense strand having 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable

double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The unexpected results, contrary to the teaching of the prior art are also clearly exemplified in **Figures 28, 29, and 30**, in which the RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps combined with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with ribo (Stab 4) or 2'-deoxy (Stab 7) purines and antisense strands having 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with phosphorothioate modifications and with ribo (Stab 5), 2'-O-methyl (Stab 8) or 2'-deoxy (Stab 11) purines) are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study. As shown in **Figures 28, 29, and 30**, the extensively and differentially modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved activity over the prior art molecules that allow these molecules to function as therapeutic modalities. The chemically modified duplexes of the instant invention are a significant and inventive advancement over the teachings of the closest prior art (Elbashir *et al.*) who teach that "more extensive" modification is detrimental to RNAi activity and whose attempts to more extensively modify such molecules resulted in *abolished* activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising and unexpected results as taught by the application as filed and priority documents, unequivocally preclude any finding of obviousness.

IV. There can be no obviousness-type double patenting issue over USSN 10/923,536

Claims 18-20 and 33-39 do not require a terminal disclaimer in view of the provisional obviousness-type double patenting rejection over Applicant's own USSN 10/923,536 because the '536 application was abandoned on July 20, 2009.

V. Conclusions

The instant claims are patentable. Applicants therefore respectfully request withdrawal of the standing rejections and allowance of the claims.

Respectfully submitted,

Date: January 20, 2010

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APPENDIX A

CLAIMS ON APPEAL

1. - 17. (Canceled)

18. A chemically modified double stranded nucleic acid molecule, wherein:

a) the double stranded nucleic acid comprises a sense strand and an antisense strand;

b) each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence;

c) the sense strand includes a terminal cap moiety at its 5'- and 3'-ends; and

d) 10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides.

19. The double stranded nucleic acid molecule of claim 18, wherein said double stranded nucleic acid molecule comprises no ribonucleotides.

20. The double stranded nucleic acid molecule of claim 18, wherein said double stranded nucleic acid molecule comprises one or more ribonucleotides.

21. - 32. (Canceled)

33. The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides.

34. The double stranded nucleic acid molecule of claim 18, wherein one or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides.

35. The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

36. The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

37. The double stranded nucleic acid molecule of claim 18, wherein one or more purine nucleotides present in said antisense strand are 2'-O-methyl purine nucleotides.

38. A composition comprising the double stranded nucleic acid molecule of claim 18 and a pharmaceutically acceptable carrier or diluent.

39. The double stranded nucleic acid molecule of claim 18, comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages.

APPENDIX B

EVIDENCE APPENDIX

None

APPENDIX C

RELATED PROCEEDINGS APPENDIX

See attached decision for Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

APPENDIX D

AMENDMENTS IN THE CLAIMS

None